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jc645 U.S. PTO

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LAW OFFICES  
EZRA SUTTON, P. A.  
A PROFESSIONAL CORPORATION  
PLAZA 9  
900 ROUTE 9

EZRA SUTTON\*  
OF COUNSEL  
ROBERT A. GREEN  
DAVID L. DAVIS

WOODBIDGE, NEW JERSEY 07095

March 23, 1999

BY EXPRESS MAIL

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CABLE: TRADEPAT  
FAX: (732) 634-3511

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Assistant Commissioner for Patents  
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File No.: TOBINICK 3.0-007 (CIP)  
Inventor(s): Dr. Edward L. Tobinick  
Title: TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE  
TREATMENT OF NEUROLOGICAL DISORDERS

Assignee: None

jc549 U.S. PTO  
09/275070  
03/23/99

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

<u>1</u> Pages of Abstract	<u>X</u> Verified Statement for Small Entity Status
<u>21</u> Pages of Specification	Declaration, Power of Attorney & Petition
<u>47</u> Number of Claims	Two (2) return-addressed postcards
<u>none</u> Sheets of Drawings	(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)
<u>none</u> Assignment for Recording (attached to copy of this letter)	
<u>X</u> PETITION TO MAKE SPECIAL; LIST OF PRIOR ART CITED BY APPLICANT; 3 PRIOR ART PATENTS; FEE (\$130)	

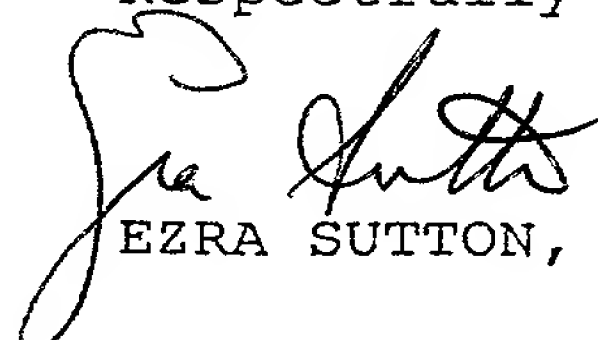
Check No. 3002 in the amount of \$753.00, calculated as follows:

Basic Fee (**Large Business \$760.00) (*Small Business \$380.00)	<u>\$380.00</u>
Additional Fees:	
Total number of claims <u>47</u>	
Total number of claims in excess of 20, <u>27</u> times (**\$18)(\$9)	<u>243.00</u>
Number of independent claims <u>2</u>	
Number of independent claims minus 3, <u>--</u> times (**\$78)(\$39)	<u>--</u>
Assignment recording fee (\$40)	<u>--</u>
Multiple dependent claims (**\$260) (\$130)	<u>--</u>
TOTAL filing and assignment recording fees	<u>\$623.00</u>
PETITION TO MAKE SPECIAL FEE	<u>130.00</u>
CONVENTION DATE _____ for _____ Appln. No. _____	<u>\$753.00</u>

is claimed.

Priority Document: \_\_\_\_\_ Enclosed \_\_\_\_\_ Will follow

Respectfully submitted,

  
EZRA SUTTON, Reg No. 25,770

ES/jmt  
Enclosures

Applicant or Patentee: Dr. Edward L. TOBINICK Attorney's  
Serial or Patent No.: Arthur J. TOBINICK Docket No.: TOBINICK  
Filed or Issued: \_\_\_\_\_ 3.0-007 (cip)  
Title: TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE  
TREATMENT OF NEUROLOGICAL DISORDERS

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY  
STATUS (37 CFR 1.2(f) AND 1.27(b) - INDEPENDENT INVENTOR**

As a below-named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark office with regard to the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

described in:  
☒ the specification filed herewith  
☐ Application Serial No. \_\_\_\_\_, filed \_\_\_\_\_  
☐ Patent No. \_\_\_\_\_, issued \_\_\_\_\_.

I have not assigned, granted, conveyed, or licensed and am under no obligation, under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

☒ no such person, concern, or organization  
☐ persons, concerns, or organizations listed below\*

\*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)


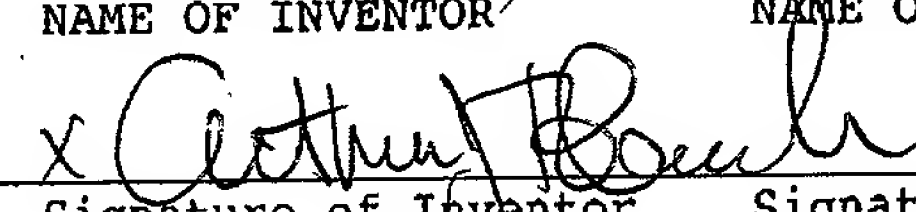
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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dr. Edward L. TOBINICK	Arthur Jerome TOBINICK	
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
		
Signature of Inventor	Signature of Inventor	Signature of Inventor
3-20-99	3-20-99	
Date	Date	Date

**TUMOR NECROSIS FACTOR ANTAGONISTS FOR  
THE TREATMENT OF NEUROLOGICAL DISORDERS**

**RELATED APPLICATION**

5           This is a continuation-in-part of Application Serial No.  
09/956,388, filed on February 24, 1999.

**FIELD OF THE INVENTION**

10           The present invention relates to tumor necrosis factor (TNF)  
antagonists or TNF blockers for the treatment of neurological  
disorders, trauma, injuries or compression; or demyelinating  
neurological disorders, including multiple sclerosis. More  
particularly, the TNF antagonists or TNF blockers, with or without  
the concurrent administration of methotrexate or Leflunomide, are  
used in a new treatment of these disorders by inhibiting the action  
of TNF in the cells of the human body. The use of these TNF  
antagonists or TNF blockers with methotrexate or Leflunomide  
results in the amelioration of these neurological conditions.

**BACKGROUND OF THE INVENTION**

20           Neurological disorders due to demyelinating disease (e.g.  
multiple sclerosis), immune disease, inflammation, trauma, or  
compression, occur in different clinical forms depending upon the  
anatomic site and the cause and natural history of the  
physiological problem. Common to all of these disorders is the  
fact that they can cause permanent neurological damage, that damage  
25           can occur rapidly and be irreversible, and that current treatment  
of these conditions is unsatisfactory, often requiring surgery

and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression, neuropathy, and pain; but also including cervical disc herniation, causing nerve compression in the neck; carpal tunnel syndrome (non-RA); acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); autoimmune disease of the nervous system; and demyelinating diseases, the most common condition being multiple sclerosis.

Steroid drugs such as cortisone that are used to treat the aforementioned neurological problems and conditions are particularly hazardous because they are used either at high dosage, with a corresponding increasing risk of side effects, or because they are used chronically, also increasing their adverse effects. Lastly, steroids are only partially effective or completely ineffective.

There remains a need for a new pharmacologic treatment of these aforementioned physiological problems of the nervous system associated with autoimmune disease, demyelinating diseases, trauma, injuries and compression with the pharmacological use of TNF antagonists or TNF blockers, which are greatly beneficial for the

large number of patients whom these conditions affect. Two new drugs which are powerful TNF blockers are etanercept and infliximab. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurologic damage mediated by TNF dependent processes occurring in the aforementioned neurological disorders. The use of these TNF antagonists or TNF blockers would result in the amelioration of these physiological neurological problems. Concurrent administration of methotrexate or Leflunomide with either etanercept or infliximab is the preferred treatment for demyelinating diseases and certain other neurological disorders.

#### DESCRIPTION OF THE PRIOR ART

Pharmacologic chemical substances, compounds and agents which are used for the treatment of neurological disorders, trauma, injuries and compression having various organic structures and metabolic functions have been disclosed in the prior art. For example, U.S. Patent Nos. 5,756,482 and 5,574,022 to ROBERTS et al disclose methods of attenuating physical damage to the nervous system and to the spinal cord after injury using steroid hormones or steroid precursors such as pregnenolone, and pregnenolone sulfate in conjunction with a non-steroidal anti-inflammatory substance such as indomethacin. These prior art patents do not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological disease, trauma, injury or compression, or autoimmune neurologic disease as in the present invention.

U.S. Patent No. 5,605,690 to JACOBS discloses a method for treating TNF-dependent inflammatory diseases such as arthritis by administering a TNF antagonist, such as soluble human TNFR (a sequence of amino acids), to a human. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological disease, trauma, injury or compression, or demyelinating neurologic disease, as in the present invention.

U.S. Patent No. 5,656,272 to LE et al discloses methods of treating TNF-alpha-mediated Crohn's disease using chimeric anti-TNF antibodies. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological trauma, injury or compression, or autoimmune neurologic disease, as in the present invention.

U.S. Patent No. 5,650,396 discloses a method of treating multiple sclerosis (MS) by blocking and inhibiting the action of TNF in a patient. This prior art patent does not teach the use of the TNF antagonist as in the present invention.

None of the prior art patents disclose or teach the use of the TNF antagonist or TNF blocker of the present invention with the concurrent administration of methotrexate or Leflunomide for suppression and inhibition of the action of TNF in a human to treat neurological disease, trauma, injury or compression, or demyelinating neurologic disease, in which the TNF antagonist gives the patient a better opportunity to heal, slows disease



progression, prevents neurological damage, or otherwise improves the patient's health.

Accordingly, it is an object of the present invention to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, for a new pharmacologic treatment of neurological disorders, trauma, injuries and compression affecting the nervous system of the human body, or demyelinating neurologic disease, such that the use of these TNF antagonists will result in the amelioration of these neurological conditions.

Another object of the present invention is to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, for providing suppression and inhibition of the action of TNF in a human to treat neurological injury, trauma or compression, or demyelinating neurologic disease.

Another object of the present invention is to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, that reduces inflammation to the patient by inhibiting the action of TNF in the human body for the immediate, short term (acute conditions) and long term (chronic conditions), such that this reduction in inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal, slows disease progression, prevents neurological damage, or otherwise improves the patient's health.

Another object of the present invention is to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, that can offer acute and chronic treatment regimens for neurological conditions caused by neurological trauma, compression, injury and/or disease, such conditions including acute spinal cord injury, herniated nucleus pulposus (herniated disc), spinal cord compression due to metastatic cancer, carpal tunnel syndrome, pituitary adenoma, primary or metastatic brain tumors, chronic pain syndromes due to metastatic tumor, increased intracranial pressure, demyelinating diseases such as multiple sclerosis, inflammatory CNS diseases, such as subacute sclerosing panencephalitis, and other related neurological disorders and diseases.

#### SUMMARY OF THE INVENTION

The present invention provides a method for inhibiting the action of TNF for treating neurological conditions in a human by administering to the human therapeutically effective doses of a TNF antagonist selected from the group consisting of etanercept and infliximab, with or without the concurrent administration of therapeutically effective doses of methotrexate or Leflunomide, for reducing the inflammation of neuronal tissue of the human and/or preventing immune system damage to neuronal tissue. The TNF antagonist is administered subcutaneously, intravenously, intrathecally, or intramuscularly; methotrexate is administered orally or intramuscularly; and Leflunomide is administered orally.



DETAILED DESCRIPTION OF THE  
PREFERRED EMBODIMENT

TNF antagonist regimens to be used for neurological disorders are designed in two general ways: acute regimens, designed to achieve rapid blood levels and rapid action, wherein TNF blockade is desired for hours to days; and chronic regimens, where TNF blockade is desired for days, weeks, or months. Currently available TNF antagonists which are suitable for these regimens are etanercept (ENBREL™) from Immunex Corporation and infliximab (REMICADE™) from Centocor, Inc. Methotrexate or Leflunomide may be administered concurrently with the TNF antagonist for demyelinating diseases and certain other neurological disorders. Methotrexate and Leflunomide produce immune system modulation, which is shown to be beneficial in the treatment of demyelinating diseases and various autoimmune diseases. Additionally, methotrexate and Leflunomide have anti-tumor effects for certain malignancies. Lastly, methotrexate and Leflunomide have direct anti-inflammatory properties.

Trauma, injury, compression and other neurological disorders can affect individual nerves, nerve roots, the spinal cord, or the brain. The conditions which are of most concern here are the following:

- 1) acute spinal cord injury,
- 2) demyelinating diseases, such as multiple sclerosis,
- 3) herniated nucleus pulposus (herniated disc),
- 4) spinal cord compression due to metastatic cancer,

- 5) carpal tunnel syndrome (non-RA),
- 6) pituitary adenoma,
- 7) primary or metastatic brain tumors,
- 8) chronic pain syndromes due to metastatic tumor,
- 5 9) increased intracranial pressure, and
- 10) inflammatory CNS diseases, such as subacute sclerosing panencephalitis.

TNF antagonists are a novel way to treat neurologic trauma, injury, compression and neurological disorders in comparison with steroids. Experimental evidence has shown that excessive levels of TNF are released by injury to neuronal tissue. Accordingly, the use of TNF antagonists will result in amelioration of these neurological conditions. Because of the profoundly powerful action of the new TNF antagonists that have recently become available, these agents can prevent neurologic injury in a unique way, filling an urgent clinical need for more effective therapy. Also, because of the extremely safe side effect profile of these agents, they can be used either singly or in combination with other pharmacologic agents, such as methotrexate or Leflunomide. TNF antagonists can also safely be used with steroids, which are the only other class of agents which have been shown to be beneficial for certain of these conditions. Importantly, the TNF antagonists lack the adverse effects of steroids as previously described. Lastly, steroids are only partially effective or completely ineffective.

More detailed discussion of each of these clinical conditions is as follows:

**1) Acute spinal cord injury:**

About 10,000 cases occur per year in the U.S., with a current population of over 200,000 patients with residual neurologic damage, many of whom are paralyzed (quadriplegia or paraplegia). Current treatment for the acute injury is inadequate. In the early 1990's it was shown that early (within 8 hours of injury) treatment with high doses of steroids (methyl prednisolone) was beneficial for some of these patients. Surgical stabilization and spinal decompression is often necessary because of excessive swelling (edema) which can itself cause further severe injury to the cord due to further compression of the cord against its bony spinal canal. The etiology of most of these cases are motor vehicle accidents, with the remainder being sports injuries, falls, and other accidents. The window of opportunity for treatment is small, since massive swelling can occur within minutes.

The treatment regimen used here would be the acute regimen. This could involve any of the TNF antagonists, but currently etanercept would be the leading candidate. Etanercept is currently approved only for rheumatoid arthritis, and is used as a subcutaneous injection of 25mg given twice a week. This regimen produces peak blood levels in an average of 72 hours. A preferred method for acute spinal cord injury involves intravenous infusion to produce a serum concentration in the range of 0.5mg/ml to 50mg/ml, such concentrations are achieved more rapidly than can be

produced by SC injection. This is a new method of dosing that is not being used for arthritis. This acute regimen is a unique delivery method for etanercept and is uniquely necessary for clinical neurologic conditions requiring rapid blockade of TNF.

5           **2) Demyelinating Disease, Such As Multiple Sclerosis:**

10           Demyelinating neurological diseases, the most important being multiple sclerosis, are inadequately treated by currently available therapies, and continue to produce progressive, severe, neurologic impairment in a large population of patients in the United States and worldwide. There is experimental evidence which documents the role of TNF in multiple sclerosis. There is a wide body of work which documents the role of both cellular and humoral immunity in multiple sclerosis. Using the new TNF antagonists etanercept and infliximab, with or without concurrent use of methotrexate or Leflunomide, represents a novel approach to the treatment of these important disorders.

15           Several novel approaches are suggested. For acute demyelinating disease, it is paramount to use therapy which is rapidly effective to prevent permanent neurological damage. In this case, novel routes of administration of the TNF antagonists may be used. These novel routes include intrathecal administration of etanercept or infliximab; or intravenous administration of etanercept. Addition of methotrexate or Leflunomide concurrently with the use of the above TNF antagonists is another novel treatment which may be used for acute demyelinating disease. For other clinical forms of demyelinating disease, the more familiar

routes of administration of etanercept (subcutaneous) or infliximab (intravenous) may be elected, with or without concurrent use of methotrexate or Leflunomide. These novel regimens are designed as such because of the complementary mechanisms of action and low toxicity of these biopharmaceutical agents.

### 3) Herniated nucleus pulposus (herniated disc):

Low back pain affects 70% of the population during their lifetime, with 25% of this group having pain in the sciatic distribution. Current pharmacologic treatment is inadequate, consisting of analgesics and anti-inflammatory medications (such as nonsteroidal anti-inflammatories (NSAIDS), such as ibuprofen (Motrin, etc.) and epidural steroid injections (generally regarded as having limited usefulness). Many of these patients eventually have surgery. Complications of lumbar disc herniation include permanent damage to the sciatic nerve, causing muscle weakness and atrophy in the lower extremity. Acute herniation with rapid onset of pain and sciatic nerve symptoms could be treated with the above acute regimen, with or without addition of the chronic regimen (described below), if symptoms continued. Treatment could also be reserved for patients not responding to conventional therapy. The acute treatment regimen, as outlined above, could be used for patients in whom rapid control of symptoms was desired. Most patients, however, would be treated conservatively and conventionally at first, with TNF blockade using one of the chronic regimens below added later for nonresponders. Herniated cervical discs would be treated the same way as herniated lumbar discs with

the need for careful evaluation by a neurologist, neurosurgeon, and/or orthopedic surgeon for signs of neurologic compromise kept in mind. The chronic treatment regimen includes subcutaneous etanercept of 25mg (dosage range 10mg to 50mg) once or twice a week; or infliximab administered by intravenous infusion once every two months (range once per month to once per six months).

#### **4) Spinal cord compression due to metastatic cancer:**

Cord compression due to metastatic cancer is a catastrophic event leading to rapid paralysis if not quickly diagnosed and treated. It is most common with cancers of the breast, colon, lung and prostate, but can be a complication of metastatic disease from a wide variety of malignancies, including melanoma and multiple myeloma. Current treatment regimens include high dose steroids, emergency radiation treatment, and/or emergent surgical decompression. Paralysis can occur within hours, so treatment must be initiated within this time period to avoid permanent sequelae. The mechanism of action of TNF blockage here would be similar to that above. In addition, it is possible that TNF blockade could be directly tumoricidal or tumoristatic with certain malignancies. Impending cord compression could be treated with the chronic regimen. However, as explained above, most patients would need to be emergently treated with the acute regimen, as outlined above.

#### **5) Carpal Tunnel Syndrome (CTS) (non-RA):**

Carpal tunnel syndrome involves compression of the median nerve at the wrist, causing pain and neurologic symptoms in the hand. It is a common condition, being aggravated by repetitive



stress injury (RSI) in the workplace (such as typists and writers, manual laborers, etc.), and is also a complication of rheumatoid arthritis (RA). Use of TNF blockade for carpal tunnel syndrome in patients with established RA would likely be covered by the existing arthritis medication for treating RA. But most patients with carpal tunnel syndrome do not have RA; they either have idiopathic CTS or CTS caused by RSI. CTS is a major cause of disability and responds poorly to current treatment regimens, which include NSAIDS, wrist splinting, and injection of steroids. The chronic treatment regimen as outlined above would be used for the treatment of CTS (non-RA type).

#### **6) Pituitary Adenoma:**

Benign pituitary tumors grow adjacent to the optic chiasm. Unrestrained growth causes compression of the optic nerve, causing visual field defects and eventuating in blindness. Treatments include radiation, surgical decompression and bromocriptine. TNF blockade could prove to be a valuable adjunctive therapy, and could be either the acute or chronic treatment regimen, depending on the clinical picture.

#### **7) Primary or Metastatic Brain Tumors:**

Primary brain tumors can be either benign (most commonly meningioma) or malignant (usually gliomas). Metastatic brain tumors can be from any source, most commonly lung cancer, breast cancer, or other malignancies such as melanoma. Treatment for these tumors is primarily surgery or radiation, with generally poor response to chemotherapy. Many of these tumors cause surrounding

edema which can cause further neurologic deterioration. TNF blockade, either the acute or chronic treatment regimen, could be beneficial while these patients are awaiting surgery. Additionally, TNF blockade, as discussed above, could have direct tumor inhibiting properties.

In an alternate treatment regimen, methotrexate orally or intramuscularly, may be administered concurrently with a TNF antagonist, wherein the dosage level of methotrexate is in the range of 2.5mg to 25mg, given from once weekly to once monthly. If the dose is given orally, the total weekly dose may be given in three equal parts over 36 hours, with 12 hours between each dose. The preferred dosage range is 7.5mg to 15mg administered weekly.

As another alternate treatment, instead of administering methotrexate, Leflunomide may be administered orally concurrently with a TNF antagonist, wherein the dosage level of Leflunomide is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg daily thereafter.

#### **8) Chronic pain syndromes due to metastatic tumor:**

Pain due to metastatic cancer is inadequately treated by currently used agents. It is probable that the mechanism of action of this pain is mediated in part by the overproduction of TNF. TNF blockade could be beneficial for selected tumors, particularly bone metastases where compression is involved. The chronic treatment regimens would be used. One general note of caution when treating malignancies is necessary: While TNF blockade is likely to have an antitumor effect with certain malignancies, it is also possible

that TNF blockade could increase growth rates with certain malignancies.

In an alternate treatment regimen, methotrexate orally or intramuscularly, may be administered concurrently with a TNF antagonist, wherein the dosage level of methotrexate is in the range of 2.5mg to 25mg, given from once weekly to once monthly.

As another alternate treatment, instead of administering methotrexate, Leflunomide may be administered orally concurrently with a TNF antagonist, wherein the dosage level of Leflunomide is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg daily thereafter.

#### **9) Elevated Intracranial Pressure (EICP):**

EICP can be idiopathic (Pseudotumor cerebri) or caused by certain drugs (vitamin A excess, isotretinoin, tetracyclines, etc.) caused by malignancy (as above), or by benign tumors (e.g. cystercircosis). TNF blockade, either the acute or chronic treatment regimen, could be helpful.

### **OPERATION OF THE PRESENT INVENTION**

#### **1) Chronic regimen dosing with etanercept**

For adults the dose is 25mg subcutaneously (range 10mg to 50mg) administered in a range of twice a week to once a month. The initial regimen being 25mg subcutaneously twice a week and for children 0.4mg/kg given twice a week. Expected serum concentrations with this regimen would be about 3.0mcg/ml, with a desired range between 0.5 and 10mcg/ml. Other routes for chronic administration could include IM or IV dosing regimens.

In an alternate treatment regimen, methotrexate orally or intramuscularly, may be administered concurrently with etanercept, wherein the dosage level of methotrexate is in the range of 2.5mg to 25mg, given from once weekly to once monthly.

5 As another alternate treatment, instead of administering methotrexate, Leflunomide may be administered orally concurrently with a TNF antagonist, wherein the dosage level of Leflunomide is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg daily thereafter.

## 10 **2) Acute regimen dosing with etanercept**

Acute treatment regimens include administration of etanercept by SC, IM, IV and intrathecal dosing routes for acute administration.

15 In an alternate treatment, methotrexate may be administered concurrently, orally or intramuscularly, wherein the dosage level is in the range of 2.5mg to 25mg, given from once weekly to once monthly. The concurrent treatment with methotrexate may be added to any of these acute treatment regimens with etanercept.

20 As another alternate treatment, instead of administering methotrexate, Leflunomide may be administered orally concurrently with a TNF antagonist, wherein the dosage level of Leflunomide is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg daily thereafter. The concurrent treatment with Leflunomide may be added to any of these acute treatment regimens  
25 with etanercept.

## **2A) Acute IV regimen with etanercept**

Etanercept is administered by IV infusion in a quantity sufficient to produce a serum concentration in the range of 0.5mg/ml to 50mg/ml.

## **2B) Acute IM regimen for etanercept**

Etanercept is given by intramuscular administration in a dose of 50mg having a range of 25mg to 100mg.

## **2C) Acute Intrathecal regimen with etanercept**

There may be clinical use for etanercept in the cerebrospinal fluid, such as for treatment of CNS lesions (demyelinating diseases, brain tumors, cord compression). Intrathecal therapy means introducing the TNF antagonist into the cerebrospinal fluid of the patient. The exact dosage is on the order of 10mg (range 1mg to 50mg).

## **3) Chronic treatment regimen with infliximab**

Chronic indications for infliximab include herniated nucleus pulposus (herniated disk), carpal tunnel syndrome, pituitary adenoma, demyelinating disease, primary or metastatic brain tumors and chronic pain syndromes due to metastatic tumor.

Usual dosage for infliximab is 5mg/kg given by IV infusion every two months with a range of 2.5mg/kg to 20mg/kg given every 2 weeks to 2 months.

In an alternate treatment regimen, methotrexate orally or intramuscularly, may be administered concurrently with infliximab, wherein the dosage level of methotrexate is in the range of 2.5mg to 25mg, given from once weekly to once monthly.

As another alternate treatment, instead of administering methotrexate, Leflunomide may be administered orally concurrently with a TNF antagonist, wherein the dosage level of Leflunomide is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg daily thereafter.

#### **4) Acute treatment regimen with infliximab**

Acute indications for infliximab include acute spinal cord injury, acute demyelinating disease, spinal cord compression and increased intracranial pressure.

The dosage for infliximab used for the acute regimen is 10mg/kg administered by IV infusion once (range 2.5mg/kg to 25mg/kg). The dose for the intrathecal administration of infliximab is 0.3mg/kg having a range of 0.1mg/kg to 1mg/kg.

In an alternate treatment, methotrexate may be administered concurrently, orally or intramuscularly, wherein the dosage level is in the range of 2.5mg to 25mg, given from once weekly to once monthly. The concurrent treatment with methotrexate may be added to any of these acute treatment regimens with infliximab.

As another alternate treatment, instead of administering methotrexate, Leflunomide may be administered orally concurrently with a TNF antagonist, wherein the dosage level of Leflunomide is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg daily thereafter. The concurrent treatment with Leflunomide may be added to any of these acute treatment regimens with infliximab.



## 5) Treatment with existing regimens

The treatment regimens of the present invention may be used in conjunction with or in place of existing treatments, such as steroids and surgery. When the treatment regimens of the present invention are used concurrently with currently available treatments, the results are additive and therefore beneficial.

### ADVANTAGES OF THE PRESENT INVENTION

Accordingly, an advantage of the present invention is that it provides a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, for a new pharmacologic treatment of neurological disorders, trauma, injuries and compression affecting the nervous system of the human body, or demyelinating neurologic disease, such that the use of these TNF antagonists will result in the amelioration of these neurological conditions.

Another advantage of the present invention is that it provides for a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, for providing suppression and inhibition of the action of TNF in a human to treat neurological injury, trauma or compression, or demyelinating neurologic disease, or inflammatory disease of the nervous system.

Another advantage of the present invention is that it provides a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, that reduces and prevents further neurological inflammation to the patient by inhibiting the action of TNF in the human body for the immediate, short term (acute

conditions) and long term (chronic conditions), such that this reduction and prevention of inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal, slows disease progression, prevents neurological damage, or otherwise improves the patient's health.

Another advantage of the present invention is that it provides for a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, that can offer acute and chronic treatment regimens for neurological conditions caused by neurological trauma, compression, injury and/or disease, such conditions including acute spinal cord injury, herniated nucleus pulposus (herniated disc), spinal cord compression due to metastatic cancer, carpal tunnel syndrome (non-RA), demyelinating disease, pituitary adenoma, primary or metastatic brain tumors, chronic pain syndromes due to metastatic tumor, increased intracranial pressure, and other related neurological disorders and diseases.

Another advantage of the present invention is to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, to treat neurologic disorders in humans either acutely or chronically by blocking the action of TNF and thereby modulating the immune response affecting neuronal tissue.

A latitude of modification, change, and substitution is intended in the foregoing disclosure, and in some instances, some features of the invention will be employed without a corresponding

use of other features. Accordingly, it is appropriate that the appended claims be construed broadly and in a manner consistent with the spirit and scope of the invention herein.

WHAT IS CLAIMED IS:

1. A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human, comprising the step of:

a) administering a therapeutically effective dosage level to said human of said TNF antagonist selected from the group consisting of etanercept and infliximab for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human.

2. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said TNF antagonist is performed subcutaneously, intravenously, intrathecally, or intramuscularly.

3. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating neurological diseases and disorders.

4. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating neurological traumas and injuries.

5. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating acute spinal cord injury.

6. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating herniated discs.

7. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating spinal cord compression.

8. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating carpal tunnel syndrome (non-RA type).

9. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating pituitary adenoma.

10. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating primary or metastatic brain tumors.

11. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating chronic pain syndrome due to metastatic tumor.

12. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating increased intracranial pressure.

13. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating central nervous system lesions.

14. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating autoimmune neurological diseases.

15. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating multiple sclerosis.

16. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said dosage level is for treating inflammatory CNS diseases such as subacute sclerosing panencephalitis.



17. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said etanercept is performed subcutaneously in said human wherein said dosage level is in the range of 10mg to 50mg for acute or chronic regimens.

5 18. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said etanercept is performed subcutaneously in said human wherein said dosage level is 25mg for acute or chronic regimens.

19. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said etanercept is performed intramuscularly in said human wherein said dosage level is in the range of 25mg to 100mg.

20. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said etanercept is performed intravenously in said human wherein said dosage level produces a serum concentration in the range of 0.5 mg/Ml to 50mg/ml.

21. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said etanercept is performed intravenously by infusion in said human wherein said dosage level produces a serum concentration of 10mg/ml.

22. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said etanercept is performed intrathecally in said human wherein said dosage level is in the range of 1mg to 50mg.

5 23. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said infliximab is performed subcutaneously in said human wherein said dosage level is in the range of 0.1mg/kg to 2.5mg/kg.

10 24. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said infliximab is performed intramuscularly in said human wherein said dosage level is in the range of 0.1mg/kg to 2.5mg/kg for acute or chronic regimens.

15 25. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said infliximab is performed intravenously in said human wherein said dosage level is in the range of 2.5mg/kg to 20 mg/kg.

20 26. A method for inhibiting the action of TNF in accordance with Claim 1, wherein the step of administering said infliximab is performed intrathecally in said human wherein said dosage level is in the range of 0.05mg/kg to 1mg/kg.

27. A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of said TNF antagonist selected from the group consisting of etanercept and infliximab for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering a therapeutically effective dosage level to said human of methotrexate or Leflunomide for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human.

28. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering are performed subcutaneously, intravenously, intrathecally, orally or intramuscularly.

29. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating neurological diseases and disorders.

30. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating primary or metastatic brain tumors.

31. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating chronic pain syndrome due to metastatic tumor.

5 32. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating central nervous system lesions.

33. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating autoimmune neurological diseases.

34. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating multiple sclerosis.

35. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the steps of administering said dosage levels are for treating inflammatory CNS diseases such as subacute sclerosing panencephalitis.

36. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said etanercept is performed subcutaneously in said human wherein said dosage level is in the range of 10mg to 50mg for acute or chronic regimens.

37. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said etanercept is performed subcutaneously in said human wherein said dosage level is 25mg for acute or chronic regimens.

5 38. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said etanercept is performed intramuscularly in said human wherein said dosage level is in the range of 25mg to 100mg.

39. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said etanercept is performed intravenously in said human wherein said dosage level produces a serum concentration in the range of 0.5mg/ml to 50mg/ml.

40. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said etanercept is performed intravenously by infusion in said human wherein said dosage level produces a serum concentration of 10mg/ml.

41. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said etanercept is performed intrathecally in said human wherein said dosage level is  
20 in the range of 1mg to 50mg.

42. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said infliximab is performed subcutaneously in said human wherein said dosage level is in the range of 0.1mg/kg to 2.5mg/kg.

43. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said infliximab is performed intramuscularly in said human wherein said dosage level is in the range of 0.1mg/kg to 2.5mg/kg for acute or chronic regimens.

44. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said infliximab is performed intravenously in said human wherein said dosage level is in the range of 2.5mg/kg to 20mg/kg.

45. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said infliximab is performed intrathecally in said human wherein said dosage level is in the range of 0.05mg/kg to 1mg/kg.

46. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said methotrexate is performed orally or intramuscularly in said human wherein said dosage level is in the range of 2.5mg to 25mg given from once weekly to once monthly.



47. A method for inhibiting the action of TNF in accordance with Claim 27, wherein the step of administering said Leflunomide is performed orally in said human wherein said dosage level is in the range of 10mg to 100mg per day for the first 3 days, and 5mg to 20mg per day thereafter.

# ABSTRACT OF THE DISCLOSURE

A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing damage to neuronal tissue or for modulating the immune response affecting neuronal tissue of the human. The TNF antagonist administered is selected from the group consisting of etanercept and infliximab. The TNF antagonist is administered subcutaneously, intravenously, intrathecally, or intramuscularly.

Methotrexate or Leflunomide may be administered concurrently with the TNF antagonist for demyelinating diseases and certain other neurological disorders.

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on \_\_\_\_\_ as  
Application Serial No. \_\_\_\_\_  
and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
_____	_____	_____	Yes	No
_____	_____	_____	Yes	No
_____	_____	_____	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>09/256,388</u>	<u>24 February 1999</u>	<u>pending</u>
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to \_\_\_\_\_ at telephone no. (732) 634-3520

Address all correspondence to \_\_\_\_\_  
EZRA SUTTON, P.A.  
Plaza 9, 900 Route 9  
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Dr. Edward L. TOBINICK  
Inventor's signature [Signature] Date 3-20-99  
Residence Los Angeles, California 90024-6903 Citizenship United States of America  
Post Office Address 100 UCLA Medical Plaza, Suite 205  
Los Angeles, California 90024-6903  
Full name of second joint inventor, if any Arthur Jerome TOBINICK  
Second Inventor's signature [Signature] Date 3-20-99  
Residence Los Angeles, California 90024-6903 Citizenship United States of America  
Post Office Address 100 UCLA Medical Plaza, Suite 205  
Los Angeles, California 90024-6903

(Supply similar information and signature for third and subsequent joint inventors.)